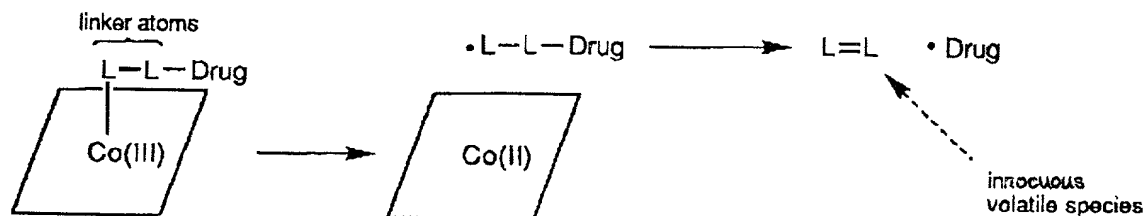
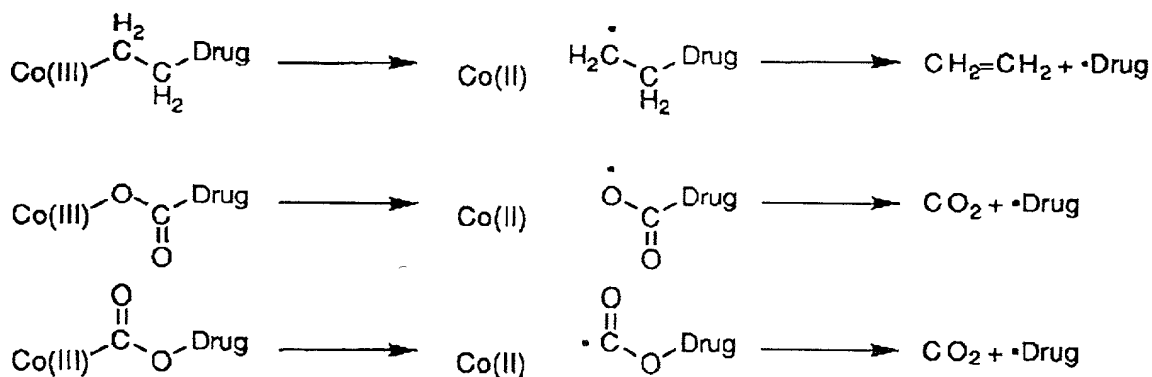


Examples of suitable spacers include, but are not limited to, polymethylene $[-(\text{CH}_2)_n]$, where n is 1-10], ester [bioactive agent attached to O and Co to C = O], carbonate, ether, acetal or any combination of two or more of these units. A skilled artisan will readily recognize other spacers which can be used in accordance with the present invention.

Several of these spacers are useful as a "self-destructing" linker group. That is, some or all of the linkage would be consumed in a fragmentation reaction. This means that, following cleavage of the C-Co bond by photolysis or sonolysis, an additional cleavage will take place several bonds away, leading to the formation of a small, unsaturated (and typically volatile) molecule made up of atoms of the former linker. This is shown schematically below:



The most typical scenario is the subsequent cleavage of a second bond, two bonds removed from the first. Thus, most self-destructive linkers would contain a two-atom unit whose extrusion as a small, gaseous molecule is favorable. Another design feature is to have the new radical species which is generated after the second cleavage step be an especially stable kind of radical. Examples of self-destructing linkers are shown below:



Targeting Molecule: a molecule which is bound by a receptor and transported into a cell by a receptor-mediated process. Examples of suitable targeting molecules include, but are not limited to, glucose, galactose, mannose, mannose 6-phosphate, transferrin,

asialoglycoprotein, α -2-macroglobulins, insulin, a peptide growth factor, cobalamin, folic acid or derivatives, biotin or derivatives, YEE(GalNAcAH)₃ or derivatives, albumin, texaphyrin, metallotexaphyrin, porphyrin, any vitamin, any coenzyme, an antibody, an antibody fragment (e.g., Fab) and a single chain antibody variable region (scFv). A skilled artisan will readily
5 recognize other targeting molecules (ligands) which bind to cell receptors and which are transported into a cell by a receptor-mediated process. The present invention is intended to include all such targeting molecules.

The present invention takes advantage of the cellular properties of cobalamin and cobalamin analogues or derivatives, as well as the cellular properties of other targeting molecules. For example, studies have shown that the absorption of physiological amounts of vitamin B₁₂ by the gut requires that it be complexed with a naturally occurring transport protein known as intrinsic factor (IF). (Castle, 1953; Fox and Castle, Allen and Majerus, 1972b). This protein is released into the lumen of the stomach by parietal cells in the fundus. Once bound to intrinsic factor, the B₁₂-IF complex interacts with a membrane bound receptor for IF located on the terminal ileum of the small intestine. The receptor-IF-B₁₂ complex is then internalized by a process of receptor-mediated endocytosis (RME). Allen and Majerus demonstrated that it is possible to chemically modify B₁₂, couple it to a resin and use the B₁₂-resin to affinity purify IF (Allen and Majerus, 1972a). This finding suggests the possibility of coupling a large macromolecule (such as the resin used by Allen and Majerus, 1972a) to B₁₂ while still
20 preserving its ability to interact specifically with intrinsic factor and thus be part of the active transport system. By coupling molecules to B₁₂ in such a way as to preserve the ability of B₁₂ to interact with intrinsic factor, it was found that the natural uptake mechanism for orally administered B₁₂ could be used to deliver various proteins, drugs or other pharmaceutically active molecules from the intestinal lumen to the circulation. It has been found that B₁₂ is
25 naturally concentrated in cancer tissue through a similar transport mechanism.

In mammals, B₁₂ is transported in the blood by transcobalamin proteins TC-I, TC-II, and TC-III. The major form of B₁₂ in the blood is methylcobalamin and the largest store of B₁₂ is adenosylcobalamin in the liver. Rapidly dividing cells, including cancer cells, require coenzyme B₁₂ for thymidine production during DNA synthesis. It has been reported by Carmel (1975) that,
30 in some patients with tumors, up to 50-fold increases in the major cobalamin transport proteins TC-I and TC-II have been observed. Waxman et al. (1972), report the finding of tumor specific